Docket No.: PF-0417-2 DIV

Response Under 37 C.F.R. 1.116 - Expedited Procedure
Examining Group 1637

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By: _____ Printed: Lyza Finuliar

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE
BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES

In re Application of: Bandman et al.

Title: VESICLE TRAFFICKING PROTEINS

Serial No.:	09/556,178	Filing Date:	April 20, 2000
Examiner:	Strzelecka, T.	Group Art Unit:	1637

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Washington, D.C. 20231

BRIEF ON APPEAL

Sir:

Further to the Notice of Appeal filed July 17, 2002, and received by the USPTO on July 23, 2002, herewith are three copies of Appellants' Brief on Appeal. Authorized fees include the $ **320.00** fee for the filing of this Brief.

This is an appeal from the decision of the Examiner finally rejecting claims 1, 2, 16, 17, 21, and 22 of the above-identified application.

(1) REAL PARTY IN INTEREST

The above-identified application is assigned of record to Incyte Pharmaceuticals, Inc. (now Incyte Genomics, Inc.) (Reel 9022, Frame 0721), which is the real party in interest herein.

(2) RELATED APPEALS AND INTERFERENCES

Appellants, their legal representative and the assignee are not aware of any related appeals or

interferences which will directly affect or be directly affected by or have a bearing on the Board's decision in the instant appeal.

(3) STATUS OF THE CLAIMS

Claims rejected:	Claims 1, 2, 16, 17, 21, and 22
Claims allowed:	(none)
Claims canceled:	(none)
Claims withdrawn:	Claims 3-15 and 18-20
Claims on Appeal:	Claims 1, 2, 16, 17, 21, and 22 (A copy of the claims on appeal, as amended, can be found in the attached Appendix).

(4) STATUS OF AMENDMENTS AFTER FINAL

There were no amendments submitted after Final Rejection.

(5) SUMMARY OF THE INVENTION

Appellants' invention is directed, *inter alia*, to polypeptides having strong homology to mouse vacuolar protein sorting homolog (GI 1703494) ("VTP-1") and compositions containing them, which have a variety of utilities, in particular in expression profiling, and in particular for diagnosis of conditions or diseases characterized by expression of VTP-1, for toxicology testing, and for drug discovery (see the Specification at, e.g., page 38, lines 22-30, and page 45, line 20 through page 46, line 7). As described in the Specification:

> Nucleic acids encoding the VTP-1 of the present invention were first identified in Incyte Clone 75871 from a THP-1 cell line cDNA library (THP1PEB01) using a computer search for amino acid sequence alignments. A consensus sequence, SEQ ID NO:2, was derived from the following overlapping and/or extended nucleic acid sequences: Incyte Clones 1396925 (BRAITUT08), 100797 (ADRENOT01), and 75871 (THP1PEB01).
>
> In one embodiment, the invention encompasses a polypeptide, VTP-1, comprising the amino acid sequence of SEQ ID NO:1, as shown in Figures 1A, 1B, 1C, 1D, 1E, 1F, and 1G. VTP-1 is 570 amino acids in length. VTP-1 has one potential amidation site encompassing residues G430-R433; one potential N-

glycosylation sites encompassing residues N522-T525; one potential cAMP- and cGMP-dependent protein kinase phosphorylation site encompassing residues K322-S325; 10 potential casein kinase II phosphorylation sites encompassing residues T40-E43, S103-D106, S109-E112, S307-D310, S351-E354, T380-D383, S441-D444, T494-D497, T511-E514, and S542-E545; and seven potential protein kinase C phosphorylation sites encompassing residues S168-K170, S343-R345, S416-K418, S441-K443, T494-R496, T563-R565, and S568-R570. As shown in Figures 2A and 2B, VTP-1 has chemical and structural homology with a mouse vacuolar protein-sorting protein, mVps45 (GI 1703494; SEQ ID NO:7). In particular, VTP-1 and mVps45 share 97% sequence homology. As illustrated by Figures 3A and 3B, VTP-1 and Vps45 have rather similar hydrophobicity plots. Northern analysis shows the expression of VTP-1 in various cDNA libraries, at least 42% of which are immortalized or cancerous, at least 24% of which involve immune response, and at least 29% are expressed in fetal/infant tissues or organs. (Specification, page 14, line 12 through page 15, line 2.)

(6) THE FINAL REJECTION

Claims 1, 2, 16, 17, 21, and 22 stand rejected under 35 U.S.C. §§ 101 and 112 based on the allegation that the claimed invention lacks patentable utility. The rejection alleges in particular that the invention is not "supported by either specific and/or substantial utility or a well established utility." (Final Office Action, page 14.)

(7) ISSUES

1. Whether claims 1, 2, 16, 17, 21, and 22 directed to vesicle trafficking protein polypeptides meet the utility requirement of 35 U.S.C. §101.

2. Whether one of ordinary skill in the art would know how to use the claimed polypeptides, e.g., in toxicology testing, drug development, and the diagnosis of disease, so as to satisfy the enablement requirement of 35 U.S.C. §112, first paragraph.

(8) GROUPING OF THE CLAIMS

As to Issue 1

All of the claims on appeal are grouped together.

As to Issue 2

All of the claims on appeal are grouped together.

(9) APPELLANTS' ARGUMENTS

The rejection of Claims 1, 2, 16, 17, 21, and 22 is improper, as the inventions of those claims have a patentable utility as set forth in the instant specification, and/or a utility well-known to one of ordinary skill in the art.

The invention at issue, identified in the patent application as vesicle trafficking protein-1, abbreviated as VTP-1, is a polypeptide encoded by a gene that is expressed in a human THP-1 cell line. The novel polypeptide is demonstrated in the specification to be a member of the class of vps45-related vesicle trafficking proteins, whose biological functions include mediating transport among the Golgi complex, synaptic vesicles, prelysosomal compartments, and the lysosome. (Specification, page 2, lines 2-4.) As such, the claimed invention has numerous practical, beneficial uses in toxicology testing, drug development, and the diagnosis of disease, none of which require knowledge of how the polypeptide actually functions. As a result of the benefits of these uses, the claimed invention already enjoys significant commercial success.

The similarity of the claimed polypeptide to another polypeptide of known, undisputed utility by itself demonstrates utility beyond the reasonable probability required by law. VTP-1 is, in that regard, homologous to mouse vacuolar protein-sorting homolog (mVps45; GI 1703494) . mVps45 is a mammalian homolog to a yeast protein, Vps45, which "is essential for transport from the Golgi to a prevacuolar compartment." (Specification, page 1, lines 16-17.) The Bandman '178 specification teaches that mammalian homologs to yeast vesicle trafficking proteins "are essential in mediating transport among the Golgi complex, synaptic vesicles, prelysosomal compartments, and the lysosome." (Specification, page 2, lines 2-4.) The Pevsner article (Pevsner, J., et al. (1996) Gene 183:7-14, Reference No. 1; incorporated by reference into the Specification) states that:

> A description of the proteins involved in lysosomal targeting is essential to understand lysosomal function in the biosynthetic and endocytic pathways, and also to understand diseases involving lysosomes. Protein trafficking to lysosomes may be disrupted in neurodegenerative disorders such as Alzheimer's disease and prion

> encephalopathies (Mayer et al., 1992; Cataldo et al., 1994) as well as organelle storage disorders diseases such as Chediak-Higashi syndrome (Zhao et al., 1994). (Reference No. 1, page 14)

In particular, the two polypeptides share 97% sequence identity over 570 amino acid residues. In addition, "[a]s illustrated by Figures 3A and 3B, VTP-1 and Vps45 have rather similar hydrophobicity plots." (Specification, page 14, lines 28-30.)

This is more than enough homology to demonstrate a reasonable probability that the utility of mVps45 can be imputed to the claimed invention. It is well-known that the probability that two unrelated polypeptides share more than 40% sequence homology over 70 amino acid residues is exceedingly small. (Brenner et. al., Proc. Natl. Acad. Sci. U.S.A. 95:6073-78 (1998); Reference No. 2). Given homology in excess of 40% over many more than 70 amino acid residues, the probability that the claimed polypeptide is related to mVps45 is, accordingly, very high. Although Appellants made similar arguments citing the Brenner paper in the Response filed January 14, 2002, the Examiner did not mention or attempt to refute these arguments in the Final Office Action. There is, in addition, direct proof of the utility of the claimed invention. Appellants submitted with the Response filed January 14, 2002 the Declaration of Furness describing some of the practical uses of the claimed invention in gene and protein expression monitoring applications as they would have been understood at the time of the patent application. The Furness Declaration describes, in particular, how the claimed polypeptide can be used in protein expression analysis techniques such as 2-D PAGE gels and western blots. Using the claimed invention with these techniques, persons of ordinary skill in the art can better assess, for example, the potential toxic affect of a drug candidate. (Furness Declaration at ¶ 10). Appellants note that the Examiner appears not to have considered the Furness Declaration as no discussion of it, beyond stating its alleged "insufficiency" at overcoming the rejections (page 2) and a one-sentence summary on page 3, appears in the Final Office Action.

The Patent Examiner contends that the claimed polypeptide cannot be useful without precise knowledge of its biological role or function. But the law never has required knowledge of biological function to prove utility. It is the claimed invention's uses, not its functions, that are the subject of a proper analysis under the utility requirement.

In any event, as demonstrated by the Furness Declaration, the person of ordinary skill in the art can achieve beneficial results from the claimed polypeptide in the absence of any knowledge as to the precise function of the protein. The uses of the claimed polypeptide for gene expression monitoring applications including toxicology testing are in fact independent of its precise function.

I. The Applicable Legal Standard

To meet the utility requirement of sections 101 and 112 of the Patent Act, the patent applicant need only show that the claimed invention is "practically useful," *Anderson v. Natta*, 480 F.2d 1392, 1397, 178 USPQ 458 (CCPA 1973) and confers a "specific benefit" on the public. *Brenner v. Manson*, 383 U.S. 519, 534-35, 148 USPQ 689 (1966). As discussed in a recent Court of Appeals for the Federal Circuit case, this threshold is not high:

> An invention is "useful" under section 101 if it is capable of providing some identifiable benefit. See *Brenner v. Manson*, 383 U.S. 519, 534 [148 USPQ 689] (1966); *Brooktree Corp. v. Advanced Micro Devices, Inc.*, 977 F.2d 1555, 1571 [24 USPQ2d 1401] (Fed. Cir. 1992) ("to violate Section 101 the claimed device must be totally incapable of achieving a useful result"); *Fuller v. Berger*, 120 F. 274, 275 (7th Cir. 1903) (test for utility is whether invention "is incapable of serving any beneficial end").

Juicy Whip Inc. v. Orange Bang Inc., 51 USPQ2d 1700 (Fed. Cir. 1999).

While an asserted utility must be described with specificity, the patent applicant need not demonstrate utility to a certainty. In *Stiftung v. Renishaw PLC*, 945 F.2d 1173, 1180, 20 USPQ2d 1094 (Fed. Cir. 1991), the United States Court of Appeals for the Federal Circuit explained:

> An invention need not be the best or only way to accomplish a certain result, and it need only be useful to some extent and in certain applications: "[T]he fact that an invention has only limited utility and is only operable in certain applications is not grounds for finding lack of utility." *Envirotech Corp. v. Al George, Inc.*, 730 F.2d 753, 762, 221 USPQ 473, 480 (Fed. Cir. 1984).

The specificity requirement is not, therefore, an onerous one. If the asserted utility is described so that a person of ordinary skill in the art would understand how to use the claimed invention, it is sufficiently specific. *See Standard Oil Co. v. Montedison, S.p.a.*, 212 U.S.P.Q. 327, 343 (3d Cir. 1981). The specificity requirement is met unless the asserted utility amounts to a "nebulous expression"

such as "biological activity" or "biological properties" that does not convey meaningful information about the utility of what is being claimed. *Cross* v. *Iizuka*, 753 F.2d 1040, 1048 (Fed. Cir. 1985).

In addition to conferring a specific benefit on the public, the benefit must also be "substantial." *Brenner*, 383 U.S. at 534. A "substantial" utility is a practical, "real-world" utility. *Nelson v. Bowler*, 626 F.2d 853, 856, 206 USPQ 881 (CCPA 1980).

If persons of ordinary skill in the art would understand that there is a "well-established" utility for the claimed invention, the threshold is met automatically and the applicant need not make any showing to demonstrate utility. Manual of Patent Examination Procedure at § 706.03(a). Only if there is no "well-established" utility for the claimed invention must the applicant demonstrate the practical benefits of the invention. *Id.*

Once the patent applicant identifies a specific utility, the claimed invention is presumed to possess it. *In re Cortright*, 165 F.3d 1353, 1357, 49 USPQ2d 1464 (Fed. Cir. 1999); *In re Brana*, 51 F.3d 1560, 1566; 34 USPQ2d 1436 (Fed. Cir. 1995). In that case, the Patent Office bears the burden of demonstrating that a person of ordinary skill in the art would reasonably doubt that the asserted utility could be achieved by the claimed invention. *Id.* To do so, the Patent Office must provide evidence or sound scientific reasoning. *See In re Langer*, 503 F.2d 1380, 1391-92, 183 USPQ 288 (CCPA 1974). If and only if the Patent Office makes such a showing, the burden shifts to the applicant to provide rebuttal evidence that would convince the person of ordinary skill that there is sufficient proof of utility. *Brana*, 51 F.3d at 1566. The applicant need only prove a "substantial likelihood" of utility; certainty is not required. *Brenner*, 383 U.S. at 532.

II. The uses of VTP-1 for toxicology testing, drug discovery, and disease diagnosis are sufficient utilities under 35 U.S.C. §§ 101 and 112, first paragraph

The claimed invention meets all of the necessary requirements for establishing a credible utility under the Patent Law: There are "well-established" uses for the claimed invention known to persons of ordinary skill in the art, and there are specific practical and beneficial uses for the invention disclosed in the patent application's specification. These uses are explained, in detail, in the Furness Declaration filed January 14, 2002. Objective evidence, not considered by the Patent Office, further corroborates

the credibility of the asserted utilities.

A. The similarity of the claimed polypeptide to another of undisputed utility demonstrates utility

It is undisputed that the claimed polypeptide is a protein having the sequence shown as SEQ ID NO:1 in the patent application and referred to as VTP-1 in that application. It is undisputed, and readily apparent from the patent application, that the claimed polypeptide shares 97% sequence identity over 570 amino acid residues with mVps45. In addition, "[a]s illustrated by Figures 3A and 3B, VTP-1 and Vps45 have rather similar hydrophobicity plots." (Specification, page 14, lines 28-30.) This is more than enough homology to demonstrate a reasonable probability that the utility of mVps45 can be imputed to the claimed invention. It is well-known that the probability that two unrelated polypeptides share more than 40% sequence homology over 70 amino acid residues is exceedingly small. Brenner et. al., Proc. Natl. Acad. Sci. U.S.A. 95:6073-78 (1998) (Reference No. 2). Given homology in excess of 40% over many more than 70 amino acid residues, the probability that the claimed polypeptide is related to mVps45 is, accordingly, very high.

Appellants have demonstrated by more than reasonable probability that VTP-1 is a member of the Vps45-related family of polypeptides, and that the Vps45-related family of polypeptides mediate transport among the Golgi complex, synaptic vesicles, prelysosomal compartments, and the lysosome. Because there is a substantial likelihood that the claimed VTP-1 is a member of the Vps45-related family of polypeptides, the members of which are indisputably useful, there is by implication a substantial likelihood that the claimed polypeptide is similarly useful. Applicants need not show any more to demonstrate utility. *In re Brana*, 51 F.3d at 1567.

The Examiner, however, alleges that:

1) The Vps45 family of polypeptides do not have utility, citing five documents; and

2) Function cannot be predicted by sequence homology.

The Examiner in the Final Office Action cites five documents to support the allegation "that VTP-1 cannot have a specific and substantial utility based on its homology to the other mVps45 proteins, since the biological significance of these proteins is not known and require [*sic*: requires] further investigation." (Final Office Action, page 11.)

In contrast to the Examiner's interpretations of the five documents, Appellants (and those of skill in the art) read them as defining a family of polypeptides with roles in vesicle trafficking. Whether or not additional research on these polypeptides is ongoing, they have a use now in vesicle trafficking and in the study of disease.

Appellants further note the h1Vps45 polypeptide discussed in the 1999 Rajasekariah document cited by the Examiner is identical to the SEQ ID NO:1 polypeptide claimed in the instant patent application. In the sentence immediately preceding that quoted on pages 10-11 of the Final Office Action, Rajasekariah et al. state "[i]n particular, the high levels of mRNA expression in heart and inflammatory cells suggests that h1Vps45 may play an important role in vesicle trafficking and inflammation." (Rajasekariah, page 693, column 1.) Rajasekariah et al. state also that h1Vps45 "may play an important role in protein trafficking as well as have clinical significance in the release of inflammatory mediators e.g., histamine, bradykinin, and cytokine release." (Rajasekariah, page 683, abstract.) Although the Rajasekariah document was published after the filing date of the Bandman 08/967,364 application (to which the instant application claims priority), it confirms the utility of the claimed polypeptides.

The Examiner further asserts that the sequence similarity between VTP-1 and mouse Vps45 is not adequate to allow one to attribute the function of mouse Vps45 to VTP-1. The Examiner alleges that:

> Absent factual evidence, a percentage sequence similarity of less than 100% is not deemed to reasonably support to one skilled in the art whether the biochemical activity of the claimed subject matter would be the same as that of such a similar known biomolecule. It is known for nucleic acids as well proteins, for example, that even a single nucleotide or amino acid change or mutation can destroy the function of the biomolecule in many instances, albeit not in all cases. The effects of these changes are largely unpredictable as to which ones have a significant effect versus not. Therefore, the citation of sequence similarity results in an unpredictable and therefore unreliable correspondence between the claimed biomolecule and the indicated similar biomolecule

> of known function and therefore lacks support regarding utility and/or enablement. Several publications document this unpredictability of the relationship between sequence and function, albeit that certain specific sequences may be found to be conserved over biomolecules of related function upon a significant amount of further research. See the following publications that support this unpredictability as well as noting certain conserved sequences in limited specific cases. (Final Office Action, pages 15-16.)

While the Examiner has cited literature (Gerhold et al., Wells et al., and Russell et al.) identifying some of the difficulties that may be involved in predicting protein function, none suggest that functional homology cannot be inferred by a reasonable probability in this case. At most, these articles individually and together stand for the proposition that it is difficult to make predictions about function with certainty. The standard applicable in this case is not, however, proof to certainty, but rather proof to reasonable probability.

Appellants made arguments against the relevance of the Gerhold et al., Wells et al., and Russell et al. documents in the Response filed January 14, 2002, but the Examiner appears not to have considered the arguments as no comments to or refutations of them were made in the Final Office Action. The Examiner merely repeats (word for word) the arguments made in the Office Action mailed August 13, 2001.

Appellants respectfully point out that the cited references do not support the Examiner's position. In the paper by Russell et al., for example, while the focus is on the conservation of protein folds rather than function, the authors do mention that "both the sequence and structure of similar proteins can evolve beyond recognition even when function is conserved." (Russell et al., page 348, column 1.) The paper by Gerhold et al. notes that homologs of human genes in organisms as diverse as fruit flies, worms, and yeast have proven to be useful in determining the functions of the human genes (see Gerhold et al, page 979). The paper by Wells et al. discloses that it is possible to identify novel members of the chemokine family "even though the overall sequence identity levels between chemokines may be as low as 20%" (Wells et al., page 546, column 1). Thus the known art clearly demonstrates that evolutionarily related proteins may exhibit considerable divergence in sequence while conserving the same overall three-dimensional structure and function. In addition, natural selection will tend to act against random mutations that alter protein structure as these would destroy or diminish

protein function; such non-functional mutated proteins will frequently result in lethal mutations and will, therefore, be selected against and eliminated from the gene-pool. One of skill in the art would therefore clearly understand that sequence similarities of far less than 100% may be reliably used to determine protein function.

The Examiner's citation of Gerhold et al. and Wells et al. with respect to the unpredictability of predicting function from sequence homology is irrelevant to the instant situation. Both references relate to the use of ESTs (fragments of genes) to predict full-length genes and their open reading frames. This does not relate to the current situation in which the polynucleotides (encoding the claimed polypeptides) are full length genes whose identity to other full length genes is based on a high degree of sequence similarity to one another.

Appellants submit that both the Revised Interim Utility Guidelines and the Revised Interim Utility Guidelines Training Materials support the use of sequence homology to known proteins to establish functional homology. The Revised Interim Utility Guidelines specifically state at page 1096, that the Examiner's decision to rebut Appellants assertion of utility:

> ---must be supported by a preponderance of all evidence of record. More specifically, when a patent application claiming a nucleic acid asserts a specific, substantial, and credible utility, and bases the assertion upon homology to existing nucleic acids or proteins having an accepted utility, the asserted utility must be accepted by the Examiner unless the Office has sufficient evidence or sound scientific reasoning to rebut such an assertion. "[A] 'rigorous correlation' need not be shown in order to establish practical utility; 'reasonable correlation' is sufficient". (emphasis added).

Clearly the PTO recognizes the well known use of sequence homology in the art to establish protein function. The Revised Interim Utility Guidelines Training Materials elaborate further on this matter in Example 10:DNA Fragment encoding a Full Open Reading Frame (ORF) at page 53, which recites a claim to a nucleic acid encoding a protein with 95% sequence identity to a known protein (a DNA ligase). The example clearly states that "there is no reason to doubt the assertion that [the claimed sequence] encodes a DNA ligase." Therefore the Revised Interim Utility Guidelines Training Materials indicate that a sequence similarity of less than 100% is deemed reasonably to support to one skilled in the art that two molecules could possess the same activity.

The Examiner must accept the applicant's demonstration that the claimed polypeptide is a member of Vps45-related protein family and that utility is proven by a reasonable probability unless the Examiner can demonstrate through evidence or sound scientific reasoning that a person of ordinary skill in the art would doubt utility. *See In re Langer*, 503 F.2d 1380, 1391-92, 183 USPQ 288 (CCPA 1974). The Examiner has not provided sufficient evidence or sound scientific reasoning to the contrary.

Nor has the Examiner provided any evidence that any member of the Vps45-related protein family, let alone a substantial number of those members, is not useful. In such circumstances the only reasonable inference is that the claimed polypeptide must be, like the other members of the Vps45-related protein family, useful.

Appellants note that regardless of the Examiner's opinion on the utility of VTP-1 based on its homology to the mouseVps45 protein, Appellants demonstrate, in the Response and Furness Declaration filed January 14, 2002 and in the instant Appeal Brief, that the claimed polypeptides also have utility in gene and protein expression monitoring applications and that this utility does not require any knowledge of the "biological significance" of the claimed polypeptides. See Section III below.

B. The uses of VTP-1 for toxicology testing, drug discovery, and disease diagnosis are practical uses that confer "specific benefits" to the public

The claimed invention has specific, substantial, real-world utility at least by virtue of its use in toxicology testing, drug development and disease diagnosis through gene expression profiling. These uses are explained in detail in the Furness Declaration filed January 14, 2002. The claimed invention is a useful tool in two-dimensional polyacrylamide gel electrophoresis ("2-D PAGE") analysis and western blots used to monitor protein expression and assess drug toxicity.

The instant application (the Bandman '178 application) is a divisional of, and claims priority to, United States patent application Serial No. 09/368,408 filed on August 4, 1999, which was itself a divisional application of and claimed priority to United States patent application Serial No. 08/967,364 filed on November 7, 1997 (hereinafter "the Bandman '364 application") having essentially the identical specification, with the exception of corrected typographical errors and reformatting. Thus page and line numbers may not match as between the Bandman '178 application and the Bandman '364 application.

In his Declaration, Mr. Furness explains the many reasons why a person skilled in the art who read the Bandman '364 application on November 7, 1997 would have understood that application to disclose the claimed polypeptide to be useful for a number of gene and protein expression monitoring applications, *e.g.*, in 2-D PAGE technologies, in connection with the development of drugs and the monitoring of the activity of such drugs. (Furness Declaration at, e.g., ¶¶ 7-13). Much, but not all, of Mr. Furness' explanation concerns the use of the claimed polypeptide in the creation of protein expression maps using 2-D PAGE.

2-D PAGE technologies were developed during the 1980's. Since the early 1990's, 2-D PAGE has been used to create maps showing the differential expression of proteins in different cell types or in similar cell types in response to drugs and potential toxic agents. Each expression pattern reveals the state of a tissue or cell type in its given environment, *e.g.*, in the presence or absence of a drug. By comparing a map of cells treated with a potential drug candidate to a map of cells not treated with the candidate, for example, the potential toxicity of a drug can be assessed. (Furness Declaration at ¶ 12.)

The claimed invention makes 2-D PAGE analysis a more powerful tool for toxicology and drug efficacy testing. A person of ordinary skill in the art can derive more information about the state or states or tissue or cell samples from 2-D PAGE analysis with the claimed invention than without it. As Mr. Furness explains:

> In view of the Bandman '364 application, . . . and other related pre-November 7, 1997 publications, persons skilled in the art on November 7, 1997 clearly would have understood the Bandman '364 application to disclose the SEQ ID NO:1 polypeptide to be useful in 2-D PAGE analyses for the development of new drugs and monitoring the activities of drugs for such purposes as evaluating their efficacy and toxicity . . . (Furness Declaration, ¶ 10)
>
> * * *
>
> Persons skilled in the art would appreciate that a 2-D PAGE map that utilized the SEQ ID NO:1 polypeptide sequence would be a more useful tool than a 2-D PAGE map that did not utilize this protein sequence in connection with conducting protein expression monitoring studies on proposed (or actual) drugs for treating inflammation and disorders associated with cell proliferation and apoptosis for such purposes as evaluating their efficacy and toxicity (Furness Declaration, ¶ 12)

Mr. Furness' observations are confirmed in the literature published before the filing of the patent application. Wilkins, for example, describes how 2-D gels are used to define proteins present in various tissues and measure their levels of expression, the data from which is in turn used in databases:

> For proteome projects, the aim of [computer-aided 2-D PAGE] analysis . . . is to catalogue all spots from the 2-D gel in a qualitative and if possible quantitative manner, so as to define the number of proteins present and their levels of expression. Reference gel images, constructed from one or more gels, for the basis of two-dimensional gel databases. (Wilkins, M.R., et al., Biotechnology and Genetic Engineering Reviews, 13: 19-50 (1995); Reference No. 3).

C. The use of proteins expressed by humans as tools for toxicology testing, drug discovery, and the diagnosis of disease is now "well-established"

The technologies made possible by expression profiling using polypeptides are now well-established. The technical literature recognizes not only the prevalence of these technologies, but also their unprecedented advantages in drug development, testing and safety assessment. These technologies include toxicology testing, as described by Furness in his Declaration.

Toxicology testing is now standard practice in the pharmaceutical industry. See, *e.g.*, John C. Rockett, et. al., Differential gene expression in drug metabolism and toxicology: practicalities, problems, and potential, Xenobiotica 29:655-691 (July 1999) (Reference No. 4):

> Knowledge of toxin-dependent regulation in target tissues is not solely an academic pursuit as much interest has been generated in the pharmaceutical industry to harness this technology in the early identification of toxic drug candidates, thereby shortening the developmental process and contributing substantially to the safety assessment of new drugs. ((Reference No. 4), page 656)

To the same effect are several other scientific publications, including Emile F. Nuwaysir, et al., Microarrays and Toxicology: The Advent of Toxicogenomics, Molecular Carcinogenesis 24:153-159 (1999) (Reference No. 5); Sandra Steiner and N. Leigh Anderson, Expression profiling in toxicology -- potentials and limitations, Toxicology Letters 112-13:467-471 (2000) (Reference No. 6).

The more genes – and, accordingly, the polypeptides they encode -- that are available for use in toxicology testing, the more powerful the technique. Control genes are carefully selected for their stability across a large set of array experiments in order to best study the effect of toxicological

compounds. See attached email from the primary investigator, Dr. Cynthia Afshari to an Incyte employee, dated July 3, 2000, as well as the original message to which she was responding (Reference No. 7). Thus, there is no expressed gene which is irrelevant to screening for toxicological effects, and all expressed genes have a utility for toxicological screening.

In fact, the potential benefit to the public, in terms of lives saved and reduced health care costs, are enormous. Recent developments provide evidence that the benefits of this information are already beginning to manifest themselves. Examples include the following:

- In 1999, CV Therapeutics, an Incyte collaborator, was able to use Incyte gene expression technology, information about the structure of a known transporter gene, and chromosomal mapping location, to identify the key gene associated with Tangier disease. This discovery took place over a matter of only a few weeks, due to the power of these new genomics technologies. The discovery received an award from the American Heart Association as one of the top 10 discoveries associated with heart disease research in 1999.

- In an April 9, 2000, article published by the Bloomberg news service, an Incyte customer stated that it had reduced the time associated with target discovery and validation from 36 months to 18 months, through use of Incyte's genomic information database. Other Incyte customers have privately reported similar experiences. The implications of this significant saving of time and expense for the number of drugs that may be developed and their cost are obvious.

- In a February 10, 2000, article in the *Wall Street Journal*, one Incyte customer stated that over 50 percent of the drug targets in its current pipeline were derived from the Incyte database. Other Incyte customers have privately reported similar experiences. By doubling the number of targets available to pharmaceutical researchers, Incyte genomic information has demonstrably accelerated the development of new drugs.

Because the Patent Examiner failed to consider the "well-established" utilities for the claimed invention in toxicology testing, drug development, and the diagnosis of disease, the Examiner's rejections should be overturned regardless of their merit.

D. Objective evidence corroborates the utilities of the claimed invention

There is in fact no restriction on the kinds of evidence a Patent Examiner may consider in

determining whether a "real-world" utility exists. "Real-world" evidence, such as evidence showing actual use or commercial success of the invention, can demonstrate conclusive proof of utility. *Raytheon v. Roper*, 220 USPQ2d 592 (Fed. Cir. 1983); *Nestle v. Eugene*, 55 F.2d 854, 856, 12 USPQ 335 (6th Cir. 1932). Indeed, proof that the invention is made, used or sold by any person or entity other than the patentee is conclusive proof of utility. *United States Steel Corp.* v. *Phillips Petroleum Co.*, 865 F.2d 1247, 1252, 9 USPQ2d 1461 (Fed. Cir. 1989).

Over the past several years, a vibrant market has developed for databases containing all expressed genes (along with the polypeptide translations of those genes). (Note that the value in these databases is enhanced by their completeness, but each sequence in them is independently valuable.) The databases sold by Appellants' assignee, Incyte, include exactly the kinds of information made possible by the claimed invention, such as tissue and disease associations. Incyte sells its database containing the sequence of the claimed polypeptide and millions of other sequences throughout the scientific community, including to pharmaceutical companies who use the information to develop new pharmaceuticals.

Both Incyte's customers and the scientific community have acknowledged that Incyte's databases have proven to be valuable in, for example, the identification and development of drug candidates. As Incyte adds information to its databases, including the information that can be generated only as a result of Incyte's discovery of the claimed polypeptide, the databases become even more powerful tools. Thus the claimed invention adds more than incremental benefit to the drug discovery and development process.

III. The Patent Examiner's Rejections Are Without Merit

Rather than responding to the evidence demonstrating utility, the Examiner attempts to dismiss it altogether by arguing that the disclosed and well-established utilities for the claimed polypeptide are not "specific and/or substantial" or "well-established" utilities. (Final Office Action at page 14.) The Examiner is incorrect both as a matter of law and as a matter of fact.

A. The Precise Biological Role Or Function Of An Expressed Polypeptide Is Not Required To Demonstrate Utility

The Patent Examiner's primary rejection of the claimed invention is based on the ground that, without information as to the precise "biological role" of the claimed invention, the claimed invention's utility is not sufficiently specific. According to the Examiner, it is not enough that a person of ordinary skill in the art could use and, in fact, would want to use the claimed invention either by itself or in a 2-D gel or western blot to monitor the expression of genes for such applications as the evaluation of a drug's efficacy and toxicity. The Examiner would require, in addition, that the applicant provide a specific and substantial interpretation of the results generated in any given expression analysis.

It may be that specific and substantial interpretations and detailed information on biological function are necessary to satisfy the requirements for publication in some technical journals, but they are not necessary to satisfy the requirements for obtaining a United States patent. The relevant question is not, as the Examiner would have it, whether it is known how or why the invention works, *In re Cortwright*, 165 F.3d 1353, 1359 (Fed. Cir. 1999), but rather whether the invention provides an "identifiable benefit" in presently available form. *Juicy Whip Inc.* v. *Orange Bang Inc.*, 185 F.3d 1364, 1366 (Fed. Cir. 1999). If the benefit exists, and there is a substantial likelihood the invention provides the benefit, it is useful. There can be no doubt, particularly in view of the Furness Declaration (at, *e.g.*, ¶¶ 10-13), that the present invention meets this test.

The threshold for determining whether an invention produces an identifiable benefit is low. *Juicy Whip*, 185 F.3d at 1366. Only those utilities that are so nebulous that a person of ordinary skill in the art would not know how to achieve an identifiable benefit and, at least according to the PTO guidelines, so-called "throwaway" utilities that are not directed to a person of ordinary skill in the art at all, do not meet the statutory requirement of utility. Utility Examination Guidelines, 66 Fed. Reg. 1092 (Jan. 5, 2001).

Knowledge of the biological function or role of a biological molecule has never been required to show real-world benefit. In its most recent explanation of its own utility guidelines, the PTO acknowledged as much (66 F.R. at 1095):

> [T]he utility of a claimed DNA does not necessarily depend on the function of the encoded gene product. A claimed DNA may have specific and substantial utility because, *e.g.*, it hybridizes near a disease-associated gene or it has gene-regulating

activity.

By implicitly requiring knowledge of biological function for any claimed polypeptide, the Examiner has, contrary to law, elevated what is at most an evidentiary factor into an absolute requirement of utility. Rather than looking to the biological role or function of the claimed invention, the Examiner should have looked first to the benefits it is alleged to provide.

B. Membership in a Class of Useful Products Can Be Proof of Utility

Despite the evidence that the claimed polypeptide is a member of both the Vps45-related protein family and the family of expressed polypeptides, whose members indisputably are useful, the Examiner refused to impute the utility of the members of the Vps45-related protein family and the family of expressed polypeptides to VTP-1. In the Office Action, the Patent Examiner takes the position that unless Appellants can identify which particular biological function within the class of Vps45-related proteins or expressed polypeptides is possessed by VTP-1, utility cannot be imputed. Further, presumably, to demonstrate any such utility by membership in the class of Vps45-related proteins or expressed polypeptides, the Examiner would require that all Vps45-related proteins or expressed polypeptides possess a "common" utility.

There is no such requirement in the law. In order to demonstrate utility by membership in a class, the law requires only that the class not contain a substantial number of useless members. So long as the class does not contain a substantial number of useless members, there is sufficient likelihood that the claimed invention will have utility and a rejection under 35 U.S.C. § 101 is improper. That is true regardless of how the claimed invention ultimately is used and whether the members of the class possess one utility or many. *See Brenner* v. *Manson*, 383 U.S. 519, 532 (1966); *Application of Kirk*, 376 F.2d 936, 943 (CCPA 1967).

Membership in a "general" class is insufficient to demonstrate utility only if the class contains a substantial number of useless members. There would be, in that case, a substantial likelihood that the claimed invention is one of the useless members of the class. In the few cases in which class membership did not prove utility by substantial likelihood, the classes did in fact include predominately useless members. *E.g.*, *Brenner* (man-made steroids); *Kirk* (same); *Natta* (man-made polyethylene

polymers).[1]

The Examiner addresses VTP-1 as if the general class in which it is included is not the Vps45-related protein family or the family of expressed polypeptides, but rather all polypeptides, including the vast majority of useless theoretical molecules not occurring in nature, and thus not pre-selected by nature to be useful. While these "general classes" may contain a substantial number of useless members, the Vps45-related protein family and the family of expressed polypeptides do not. The Vps45-related protein family and the family of expressed polypeptides are sufficiently specific to rule out any reasonable possibility that VTP-1 would not also be useful like the other members of the family.

Because the Examiner has not presented any evidence that the Vps45-related and expressed classes of polypeptides have any, let alone a substantial number, of useless members, the Examiner must conclude that there is a "substantial likelihood" that the claimed polypeptide is useful.

Even if the Examiner's "common utility" criterion were correct – and it is not – the Vps45-related and expressed polypeptide families would meet it. Known members of the Vps45-related protein family mediate transport among the Golgi complex, synaptic vesicles, prelysosomal compartments, and the lysosome. A person of ordinary skill in the art need not know any more about how the claimed invention mediates transport among the Golgi complex, synaptic vesicles, prelysosomal compartments, and the lysosome to use it, and the Examiner presents no evidence to the contrary.

As demonstrated by Appellants, knowledge that VTP-1 is a Vps45-related protein and an expressed polypeptide is more than sufficient to make it useful for the diagnosis and treatment of inflammation and disorders associated with cell proliferation and apoptosis. Indeed, VTP-1 has been shown to be expressed in tissues associated with cancer, inflammation, and fetal/infant development. (Specification, page 27, lines 27-29.) The Examiner must accept these facts to be true unless the Examiner can provide evidence or sound scientific reasoning to the contrary. But the Examiner has not done so.

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[1]At a recent Biotechnology Customer Partnership Meeting, PTO Senior Examiner James Martinell described an analytical framework roughly consistent with this analysis. He stated that when an applicant's claimed protein "is a member of a family of proteins that already are known based upon sequence homology," that can be an effective assertion of utility.

C. The uses of VTP-1 in toxicology testing, drug discovery, and disease diagnosis are practical uses beyond mere study of the invention itself

There is no authority for the proposition that use as a tool for research is not a substantial utility. Indeed, the Patent Office itself has recognized that just because an invention is used in a research setting does not mean that it lacks utility (Section 2107.01 of the Manual of Patent Examining Procedure, 8th Edition, August 2001, under the heading I. Specific and Substantial Requirements, Research Tools):

> Many research tools such as gas chromatographs, screening assays, and nucleotide sequencing techniques have a clear, specific and unquestionable utility (e.g., they are useful in analyzing compounds). An assessment that focuses on whether an invention is useful only in a research setting thus does not address whether the specific invention is in fact "useful" in a patent sense. Instead, Office personnel must distinguish between inventions that have a specifically identified substantial utility and inventions whose asserted utility requires further research to identify or reasonably confirm.

The PTO's actual practice has been, at least until the present, consistent with that approach. It has routinely issued patents for inventions whose only use is to facilitate research, such as DNA ligases, acknowledged by the PTO's Training Materials to be useful.

The subset of research uses that are not "substantial" utilities is limited. It consists only of those uses in which the claimed invention is to be an **object** of further study, thus merely inviting further research on the invention itself. This follows from *Brenner*, in which the U.S. Supreme Court held that a process for making a compound does not confer a substantial benefit where the only known use of the compound was to be the object of further research to determine its use. *Id.* at 535. Similarly, in *Kirk*, the Court held that a compound would not confer substantial benefit on the public merely because it might be used to synthesize some other, unknown compound that would confer substantial benefit. *Kirk*, 376 F.2d at 940, 945. ("What appellants are really saying to those in the art is take these steroids, experiment, and find what use they do have as medicines.") Nowhere do those cases state or imply, however, that a material cannot be patentable if it has some other, additional beneficial use in research.

Such beneficial uses beyond studying the claimed invention itself have been demonstrated, in particular those described in the Furness Declaration. The Furness Declaration demonstrates that the

claimed invention is a tool, rather than an object, of research, and it demonstrates exactly how that tool is used. Without the claimed invention, it would be more difficult to generate information regarding the properties of tissues, cells, drug candidates and toxins apart from additional information about the polypeptide itself.

The claimed invention has numerous other uses as a research tool, each of which alone is a "substantial utility." These include uses in diagnostics and drug screening (Specification, page 38, lines 13-30 and page 45, line 20 through page 46, line 7.)

D. The Patent Examiner Failed to Demonstrate That a Person of Ordinary Skill in the Art Would Reasonably Doubt the Utility of the Claimed Invention in Toxicology Testing

1. Toxicology testing is a specific, substantial and credible utility

The Examiner argues that "[e]ven if the expression of Aplicant's [*sic*] individual polypeptide is affected by a test compound for drug screening, the specification does not disclose any specific and substantial interpretation for the result, and none is known in the art." (Final Office Action, page 12.)

Contrary to the Examiner's allegation, there is indeed a "specific and substantial" interpretation for the results of toxicology testing using the claimed polypeptide. Monitoring the expression of the claimed polypeptides is a method of testing the toxicology of drug candidates during the drug development process. Mr. Furness in his Declaration states that "good drugs are not only potent, they are specific. This means that they have strong effects on a specific biological target and minimal effects on all other biological targets." (Furness Declaration ¶ 10.) Thus, if the expression of a particular polypeptide is affected in any way by exposure to a test compound, and if that particular polypeptide is not the specific target of the test compound (e.g., if the test compound is a drug candidate), then the change in expression is an indication that the test compound has undesirable toxic side effects. It is important to note that such an indication of possible toxicity is specific not only for each compound tested, but also for each and every individual polypeptide sequence whose expression is being monitored.

However, the Examiner continues to view the utility of the claimed polypeptides in toxicology

testing as requiring knowledge of either the biological function or disease association of the polypeptides. The Examiner views toxicology testing as a process to measure the toxicity of a drug candidate only when that drug candidate is specifically targeted to the claimed polypeptides. The Examiner has refused to consider that the claimed polypeptides are useful for measuring the toxicity of drug candidates which are targeted not to the claimed polypeptides, but to other polypeptides. This utility of the claimed polypeptides does not require any knowledge of the biological function or disease association of the polypeptides, and is a specific, substantial and credible utility.

The Examiner argues on page 12 of the Final Office Action that the utilities disclosed in the specification for gene and protein expression monitoring are not specific. The Examiner's argument amounts to nothing more than the Examiner's disagreement with the Furness Declaration and the Appellants' assertions about the knowledge of a person of ordinary skill in the art, and is tantamount to the substitution of the Examiner's own judgment for that of the Appellants' expert. The Examiner must accept the Appellants' assertions to be true. The Examiner is, moreover, wrong on the facts because the Furness Declaration demonstrates how one of skill in the art, reading the specification at the time the Bandman '364 application was filed (November 7, 1997), would have understood that specification to disclose the use of the claimed polypeptides in gene expression monitoring for toxicology testing, drug development, and the diagnosis of disease (See the Furness Declaration at, e.g., ¶¶ 9-13).

2. Irrelevance of disease association or differential expression to utility in toxicology testing

The Examiner asserts that the specification does not disclose an association of the claimed polypeptides with "any disease or disorder" (page 8) and does not disclose that "a difference in the level [*sic*: of] VTP-1 expression as compared with normal tissues" (page 8), and therefore that "any information obtained from an expression profile would only serve as the basis for further research on the observation itself." (Final Office Action, page 9.)

These are irrelevant. Appellants need not demonstrate whether the claimed polypeptides are associated with disease, can be used to treat or prevent any disease, or whether the claimed polypeptides are differentially expressed. Appellants need only demonstrate that the claimed

polypeptides are useful.

The claimed polypeptides can be used for toxicology testing in drug discovery without any knowledge of disease association or differential expression. Monitoring the expression of the claimed polypeptides gives important information on the potential toxicity of a drug candidate that is specifically targeted to any other polypeptide, regardless of the disease association or differential expression of the claimed polypeptides. The claimed polypeptides are useful for measuring the toxicity of drug candidates specifically targeted to other polypeptides, regardless of any possible utility for measuring the properties of the claimed polypeptides.

On pages 8-9 of the Final Office Action, the Examiner argues that "in the absence of any disclosed relationship between the claimed polynucleotide[2] or the protein that is encoded thereby and any disease or disorder and the lack of any correlation between the claimed polynucleotide or the encoded protein with any known disease or disorder, any information obtained from an expression profile would only serve as the basis for further research on the observation itself."

As discussed above, the claimed polypeptides are useful for measuring the toxicity of drug candidates specifically targeted to polypeptides other than the claimed polypeptides. Knowledge of disease association of the claimed polypeptides is not necessary for using these claimed polypeptides as research tools in such toxicology testing.

3. Discussion of toxicology testing in the Specification

The Examiner alleges that "toxicology testing and drug discover [*sic*] are not specifically recited" and that "the particulars of toxicology testing with SEQ ID NO:1 are not disclosed in the instant specification." (Final Office Action, page 11.) Well-established utilities, such as toxicology testing, need not be explicitly disclosed in a patent application. Furthermore, the Examiner's position amounts to nothing more than the Examiner's disagreement with the Furness Declaration (which

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[2]The Examiner in this sentence twice refers to the "claimed polynucleotide." (Final Office Action, pages 8-9.) Appellants note that the claims on appeal are directed to polypeptides, not polynucleotides, and respectfully suggest that the Examiner's reference to the "claimed polynucleotide" is inadvertent.

purports therefore to substitute the Examiner's judgment for that of Appellants' expert) and Appellants' assertions about the knowledge of a person of ordinary skill. The Examiner must accept Appellants' assertions to be true. The Final Office Action fails to address the disclosure in the instant specification on gene and protein expression monitoring applications, as discussed below.

Support for the utility of the claimed sequences in toxicology testing, as well as for utility in drug screening, may be found in the specification. For example, "protein bioassay or immunoassay techniques which include membrane, solution, or chip based technologies" may be used "for the detection and/or quantification of nucleic acid or protein." (Bandman '178 application at page 25, lines 24-26) Further:

> A variety of protocols including ELISA, RIA, and FACS for measuring VTP are known in the art and provide a basis for diagnosing altered or abnormal levels of VTP expression. Normal or standard values for VTP expression are established by combining body fluids or cell extracts taken from normal mammalian subjects, preferably human, with antibody to VTP under conditions suitable for complex formation The amount of standard complex formation may be quantified by various methods, but preferably by photometric, means. Quantities of VTP expressed in subject, control and disease, samples from biopsied tissues are compared with the standard values. Deviation between standard and subject values establishes the parameters for diagnosing disease. (Bandman '178 application at page 38, lines 22-30.)

Moreover, the Bandman '178 application discloses that "VTP, its catalytic or immunogenic fragments or oligopeptides thereof, can be used for screening libraries of compounds in any of a variety of drug screening techniques" and that "one may use competitive drug screening assays in which neutralizing antibodies capable of binding VTP specifically compete with a test compound for binding VTP." (Bandman '178 application, page 45, lines 20-22 and page 46, lines 4-6.)

4. Utility of all expressed polypeptides in toxicology testing

The Examiner asserts that use as a control for toxicology testing is not specific and substantial, and therefore not well-established, because it "would apply to virtually every member of a general class of materials, such as any collection of proteins, but is only potential with respect to SEQ ID NO:1."

(Final Office Action, pages 11-12). Mr. Furness, in his Declaration, states that "the specification of the Bandman '364 patent application disclosed to a person skilled in the art at the time of its filing a number of substantial, specific and credible real-world utilities for the claimed SEQ ID NO:1 polypeptide." (Furness Declaration, ¶6.) The Examiner does not point to any law, however, that says a utility that is shared by a large class is somehow not a utility. If all of the class of proteins can be so used, then they all have utility. The issue is, once again, whether the claimed invention has any utility, not whether other compounds have a similar utility. Nothing in the law says that an invention must have a "unique" utility. Indeed, the whole notion of "well established" utilities presupposes that many different inventions can have the exact same utility. If the Examiner's argument was correct, there could never be a well established utility, because you could always find a generic group with the same utility!

Furthermore, the Examiner is incorrect in stating that "virtually every member of a general class of materials, such as any collection of proteins" could be used in toxicology testing (Final Office Action, pages 11-12). The property of the claimed polypeptides that makes them useful as controls for toxicology testing is their expression in naturally occurring cells. A polypeptide having a random, non-naturally occurring sequence would most likely not be useful as a control for toxicology testing.

The Examiner further asserts that "the information that is gained from the gels is dependent on the pattern derived from the gels, and says nothing with regard to each individual protein spot on the gels" and that this is, again, a general utility (Final Office Action, page 12). Appellants note that while the information derived from a 2-D PAGE gel does depend upon the pattern derived from multiple spots on the gel, a 2-D PAGE gel still cannot be made without individual members. Thus each individual polypeptide sequence has a utility in creating 2-D PAGE gels. Each of these individual polypeptides has a unique and specific utility in that it records the expression level of a unique gene or protein. This is a substantial, "real world" utility in that one of ordinary skill in the art would know how to use the polypeptide sequences in a 2-D PAGE gel, without any further experimentation.

The Examiner alleges that "the efficacy (ability of producing a desired effect) of a drug compound could not be evaluated from the 2-D PAGE gel map because there is no way to assess the meaning of any individual hit from this procedure. The first requirement is that one must know the biological significance of the polypeptide(s) which is(are) being evaluated." (Final Office Action, page

13.) Mr. Furness in his Declaration states that "[e]xpressed proteins are useful for 2-D PAGE analysis in toxicology expression studies for a variety of reasons, particularly for purposes relating to providing controls for the 2-D PAGE analysis, and for identifying sequence or post-translational variants of the expressed sequences in response to exogenous compounds. (Furness Declaration, ¶12.) The "meaning" of each individual hit is that the drug being tested altered the expression of an individual protein. If this protein is not the polypeptide targeted by the drug, then the drug may have potential side effects that may limit its usefulness as a specific drug. Learning this from a 2-D PAGE protein expression monitoring experiment early in the drug development process costs less than learning this, for example, during Phase III clinical trials. The Examiner provides neither evidence nor sound scientific reasoning, only unsupported personal opinion, to support the allegation that knowledge of "biological significance" is required for toxicology testing.

E. The Patent Examiner Failed to Demonstrate That a Person of Ordinary Skill in the Art Would Reasonably Doubt the Utility of the Claimed Invention Based on Homology to Mouse Vps45

Based principally on citations to scientific literature identifying some of the difficulties involved in predicting protein function, the Examiner rejected the pending claims on the ground that the applicant cannot impute utility to the claimed invention based on its 97% homology to mouse Vps45. The Examiner's rejection is both incorrect as a matter of fact and as a matter of procedural law.

As demonstrated in § III.B.1., *supra*, the literature cited by the Examiner is not inconsistent with the Appellants' proof of homology by a reasonable probability. It may show that Appellants cannot prove function by homology with **certainty**, but Appellants need not meet such a rigorous standard of proof. Under the applicable law, once the applicant demonstrates a *prima facie* case of homology, the Examiner must accept the assertion of utility to be true unless the Examiner comes forward with evidence showing a person of ordinary skill would doubt the asserted utility could be achieved by a reasonable probability. *See In re Brana*, 51 F.3d at 1566; *In re Langer*, 503 F.2d 1380, 1391-92, 183 USPQ 288 (CCPA 1974). The Examiner has not made such a showing and, as such, the Examiner's rejection should be overturned.

IV. By Requiring the Patent Applicant to Assert a Particular or Unique Utility, the Patent Examination Utility Guidelines and Training Materials Applied by the Patent Examiner Misstate the Law

There is an additional, independent reason to overturn the rejections: to the extent the rejections are based on Revised Interim Utility Examination Guidelines (64 FR 71427, December 21, 1999), the final Utility Examination Guidelines (66 FR 1092, January 5, 2001) and/or the Revised Interim Utility Guidelines Training Materials (USPTO Website www.uspto.gov, March 1, 2000), the Guidelines and Training Materials are themselves inconsistent with the law.

The Training Materials, which direct the Examiners regarding how to apply the Utility Guidelines, address the issue of specificity with reference to two kinds of asserted utilities: "specific" utilities, which meet the statutory requirements, and "general" utilities, which do not. The Training Materials define a "specific utility" as follows:

> A [specific utility] is *specific* to the subject matter claimed. This contrasts to *general* utility that would be applicable to the broad class of invention. For example, a claim to a polynucleotide whose use is disclosed simply as "gene probe" or "chromosome marker" would not be considered to be specific in the absence of a disclosure of a specific DNA target. Similarly, a general statement of diagnostic utility, such as diagnosing an unspecified disease, would ordinarily be insufficient absent a disclosure of what condition can be diagnosed.

The Training Materials distinguish between "specific" and "general" utilities by assessing whether the asserted utility is sufficiently "particular," *i.e.*, unique (Training Materials at p.52) as compared to the "broad class of invention." (In this regard, the Training Materials appear to parallel the view set forth in Stephen G. Kunin, Written Description Guidelines and Utility Guidelines, 82 J.P.T.O.S. 77, 97 (Feb. 2000) ("With regard to the issue of specific utility the question to ask is whether or not a utility set forth in the specification is *particular* to the claimed invention.").)

Such "unique" or "particular" utilities never have been required by the law. To meet the utility requirement, the invention need only be "practically useful," *Natta*, 480 F.2d 1 at 1397, and confer a "specific benefit" on the public. *Brenner*, 383 U.S. at 534. Thus incredible "throwaway" utilities, such as trying to "patent a transgenic mouse by saying it makes great snake food," do not meet this standard.

Karen Hall, Genomic Warfare, The American Lawyer 68 (June 2000) (quoting John Doll, Chief of the Biotech Section of USPTO).

This does not preclude, however, a general utility, contrary to the statement in the Training Materials where "specific utility" is defined (page 5). Practical real-world uses are not limited to uses that are unique to an invention. The law requires that the practical utility be "definite," not particular. *Montedison,* 664 F.2d at 375. Appellant is not aware of any court that has rejected an assertion of utility on the grounds that it is not "particular" or "unique" to the specific invention. Where courts have found utility to be too "general," it has been in those cases in which the asserted utility in the patent disclosure was not a practical use that conferred a specific benefit. That is, a person of ordinary skill in the art would have been left to guess as to how to benefit at all from the invention. In *Kirk*, for example, the CCPA held the assertion that a man-made steroid had "useful biological activity" was insufficient where there was no information in the specification as to how that biological activity could be practically used. *Kirk*, 376 F.2d at 941.

The fact that an invention can have a particular use does not provide a basis for requiring a particular use. *See Brana, supra* (disclosure describing a claimed antitumor compound as being homologous to an antitumor compound having activity against a "particular" type of cancer was determined to satisfy the specificity requirement). "Particularity" is not and never has been the *sine qua non* of utility; it is, at most, one of many factors to be considered.

As described *supra*, broad classes of inventions can satisfy the utility requirement so long as a person of ordinary skill in the art would understand how to achieve a practical benefit from knowledge of the class. Only classes that encompass a significant portion of nonuseful members would fail to meet the utility requirement. *Supra* § III.B. (*Montedison,* 664 F.2d at 374-75).

The Training Materials fail to distinguish between broad classes that convey information of practical utility and those that do not, lumping all of them into the latter, unpatentable category of "general" utilities. As a result, the Training Materials paint with too broad a brush. Rigorously applied, they would render unpatentable whole categories of inventions heretofore considered to be patentable, and that have indisputably benefitted the public, including the claimed invention. *See supra* § III.B. Thus the Training Materials cannot be applied consistently with the law.

V. To the extent the rejection of the claimed invention under 35 U.S.C. § 112, first paragraph, is based on the improper rejection for lack of utility under 35 U.S.C. § 101, it must be reversed.

The rejection set forth in the Office Action is based on the assertions discussed above, i.e., that the claimed invention lacks patentable utility. To the extent that the rejection under § 112, first paragraph, is based on the improper allegation of lack of patentable utility under § 101, it fails for the same reasons.

(10) CONCLUSION

Appellants respectfully submit that rejections for lack of utility based, *inter alia*, on an allegation of "lack of specificity," as set forth in the Office Action and as justified in the Revised Interim and final Utility Guidelines and Training Materials, are not supported in the law. Neither are they scientifically correct, nor supported by any evidence or sound scientific reasoning. These rejections are alleged to be founded on facts in court cases such as *Brenner* and *Kirk*, yet those facts are clearly distinguishable from the facts of the instant application, and indeed most if not all nucleotide and protein sequence applications. Nevertheless, the PTO is attempting to mold the facts and holdings of these prior cases, "like a nose of wax,"[3] to target rejections of claims to polypeptides and polynucleotides, where biological activity information has not been proven by laboratory experimentation, and they have done so by ignoring perfectly acceptable utilities fully disclosed in the specifications as well as well-established utilities known to those of skill in the art. As is disclosed in the specification, and even more clearly, as one of ordinary skill in the art would understand, the claimed invention has well-established, specific, substantial and credible utilities. The rejections are, therefore, improper and should be reversed.

Moreover, to the extent the above rejections were based on the Revised Interim and final Examination Guidelines and Training Materials, those portions of the Guidelines and Training Materials that form the basis for the rejections should be determined to be inconsistent with the law.

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[3]"The concept of patentable subject matter under §101 is not 'like a nose of wax which may be turned and twisted in any direction * * *.' *White v. Dunbar*, 119 U.S. 47, 51." *(Parker v. Flook,* 198 USPQ 193 (US SupCt 1978))

Due to the urgency of this matter and its economic and public health implications, an expedited review of this appeal is earnestly solicited.

If the USPTO determines that any additional fees are due, the Commissioner is hereby authorized to charge Deposit Account No. **09-0108.**

This brief is enclosed in triplicate.

Respectfully submitted,

INCYTE GENOMICS, INC.

Date: September 23, 2002

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APPENDIX - CLAIMS ON APPEAL

1. (As Amended) An isolated polypeptide comprising an amino acid sequence selected from the group consisting of:

a) an amino acid sequence selected from the group consisting of SEQ ID NO:1, SEQ ID NO:3, and SEQ ID NO:5,

b) a naturally-occurring amino acid sequence having at least 90% sequence identity to an amino acid sequence selected from the group consisting of SEQ ID NO:3 and SEQ ID NO:5,

c) a biologically-active fragment of an amino acid sequence selected from the group consisting of SEQ ID NO:1, SEQ ID NO:3, and SEQ ID NO:5,

d) an immunogenic fragment of an amino acid sequence selected from the group consisting of SEQ ID NO:1, SEQ ID NO:3, and SEQ ID NO:5, and

e) a naturally-occurring amino acid sequence having at least 98% sequence identity to the amino acid sequence of SEQ ID NO:1.

2. (As Amended) An isolated polypeptide of claim 1, comprising an amino acid sequence selected from the group consisting of SEQ ID NO:1, SEQ ID NO:3, and SEQ ID NO:5.

16. (As Amended) A composition comprising an a polypeptide of claim 1 and a pharmaceutically acceptable excipient.

17. (As Amended) A composition of claim 16, wherein the polypeptide comprises an amino acid sequence selected from the group consisting of SEQ ID NO:1, SEQ ID NO:3, and SEQ ID NO:5.

21. (Reiterated) An isolated polypeptide of claim 1, comprising the amino acid sequence of SEQ ID NO:1.

22. (Reiterated) A composition of claim 16, wherein the polypeptide comprises the amino acid sequence of SEQ ID NO:1.